European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 07, 2020

Advanced Glycation End-Products In Diabetes Complications

Anush N[a,b], Bineesh C. P.[b,c], Jeena Gupta[d], Pranav Kumar Prabhakar[b, *]

[a]*Vocational Teacher in MLT, Sree Narayana Vocational Higher secondary School, Sreekanteswaram, Cherthala, Kerala, India-688526*
[b]*School of Applied Medical Science, Lovely Professional University, Phagwara Punjab-144411*
[c]*Department of Medical Biochemistry, Co-operative Institute of Healh Sciences, Thalassery, Kerala 670101*
[d]*Department of Biochemistry, Lovely Professional University Punjab, India 144411*

Emai: pranav.16113@lpu.co.in

Abstract: Diabetic complications, such as, retinopathy, nephropathy lead to blindness and end stage renal failure respectively, various neuropathies, and ultimately increased mortality. While the exact mechanisms that lie behind the pathological changes associated with diabetes remain obscure, however, it is widely believed that chronic or intermittent hyperglycemia may alter various metabolic pathways at the tissue level, for instance, increased flux through the polyol and the hexosamine pathways as well as a persistent activation of protein kinase C (PKC). Reducing sugars such as glucose and fructose may react non-enzymatically through their carbonyl groups with free amino groups of proteins (commonly the Ɛ amino group of lysine) to form a Schiff base intermediate which then rearranges to a more stable structure known as Amadori product. The Amadori products generated by the aforementioned Maillard reaction may then undergo further reactions, including dehydration, oxidation and rearrangement resulting in the irreversible formation of heterogeneous advanced glycation end products (AGEs).

Keywords: Diabetes; protein kinase; complications; hyperglycemia; glucose; hexosamine

1. INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia and other metabolic aberrations, which together contribute to micro- and macro-vascular complications and organ dysfunction. Diabetic complications, such as, retinopathy, nephropathy lead to blindness and end stage renal failure respectively, various neuropathies, and ultimately increased mortality. Large scale studies such as the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have evaluated the effect of long term hyperglycemia and glycemic control. While the exact mechanisms that lie behind the pathological changes associated with diabetes remain obscure, however, it is widely believed that chronic or intermittent hyperglycemia may alter various metabolic pathways at the tissue level, for instance, increased flux through the polyol and the hexosamine pathways as well as a persistent activation of protein kinase C (PKC). These aberrations may lead to formation of glycation adducts and oxidative stress, inducing inflammation and precipitating apoptosis or cellular death.

Advanced Glycation End-products (AGEs)

Reducing sugars such as glucose and fructose may react non-enzymatically through their carbonyl groups with free amino groups of proteins (commonly the Ɛ amino group of lysine) to form a Schiff base intermediate which then rearranges to a more stable structure known as Amadori product. The Amadori products generated by the aforementioned Maillard reaction may then undergo further reactions, including dehydration, oxidation and rearrangement resulting in the irreversible formation of heterogeneous advanced glycation end products (AGEs). In addition to proteins, such covalent adducts may be formed with lipids as well as nucleic acids since the amino groups of adenine and guanine are also susceptible to glycation reactions (Vlassara, 1996; Baynes, 2002). Advanced glycation modifies these macromolecules in an irreparable manner, adversely affecting and compromising their structural and functional roles (Brownlee, 1995; Shah and Brownlee, 2016; Sharma et al., 2019). Moreover, oxidative or dicarbonyl stress may trigger oxidation or degradation of glucose to yield dicarbonyl compounds including, but not limited to glyoxal, glyceraldehyde, glycolaldehyde, that may also participate in glycation reactions generating AGEs (Goldin et al., 2006; Prabhakar et al., 2020) which are reported to accumulate intracellularly (Giardino et al., 1994; Sharma et al., 2019). Originally, glycation end products were characterized as fluorescent brown-coloured substances with cross-linking abilities, however, subsequently AGEs such as N-carboxymethylysine (CML), which is the major AGE in vivo, have been identified that are colourless and non-fluorescent with no significant ability to cross-link (Baynes and Thorpe, 1999; Singh, 2012). On the basis of their origin, AGEs have been classified as (i) AGE-1, for glucose-derived glycation products, (ii) AGE-2, glyceraldehyde-derived, (iii) AGE-3, glycoaldehyde-derived, (iv) AGE-4, methylglyoxal derived AGEs, (v) AGE-5, glyoxal-derived AGEs, and (vi) AGE-6, 3-deoxyglucosone-derived AGEs (Sato et al., 2006). In fact, specific autoantibodies have been detected against these classes of AGEs in the serum of diabetic patients (Turk et al., 2001; Miura et al., 2004).

Dietary AGEs

Furthermore, there is evidence that AGEs may also be exogenously ingested, with high fat, high protein animal-derived foods being rich in AGEs and likely to form AGEs during the cooking process (Uribarri et al., 2005; Singh et al., 2016; 2018). While dietary AGEs have been reported to constitute 6-7% of the total AGEs pool and shown to induce inflammation in healthy human subjects (Uribarri et al., 2005), however, other groups have debated the role played by dietarily derived AGEs (Lueovano-Contreras et al., 2010; Poulsen et al., 2013) with reports of limited absorption of dietary AGEs and vegetarians having higher AGEs than non-vegetarians. Nonetheless, a diet restricted in food-derived AGEs are considered to inhibit vascular complications in diabetic patients (Uribarri et al., 2010; Lueovano-Contreras et al., 2013) with experimental evidence indicating that long-term dietary AGEs restriction was associated with lowered insulin resistance and oxidative stress. A large prospective study of American women who regularly consumed red meat found increased diabetes risk with the use of cooking methods known to promote browning reactions (Liu et al., 2017; Tandon et al., 2018a, 2018b, 2019). Separate studies on decreasing the amount of food-derived AGE intake in diabetic patients reported a drop in serum levels of AGEs within 2-6 weeks, resulting in a lowering of markers for vascular complications such as C-reactive protein (Luevano-Contreras et al., 2013; Vaid et al., 2014) and inhibition of oxidative degeneration of blood LDL-cholesterol reducing the risk of vascular complications (Wu et al., 2011; Vyas, 2019; Usman et al., 2019). However, various factors such as, differing absorption of AGEs by the gut, ability to bind the receptor for AGEs as well as the type of AGEs, ought to be given due consideration before concluding the evidence of the positive impact of AGE-limiting diets (Yadav et al., 2011; Rhee and Kim, 2018).

AGEs accumulation

AGEs have been found to accumulate in tissues from diabetic patients (Vlassara, 1996; Brownlee, 1995), particularly at sites of diabetic complications, including retina, kidney and atherosclerotic plaques (Hammes et al., 1999). Pugliese (2008) noted that the intracellular accumulation of AGEs may modulate cytoplasmic and nuclear factors, including transcription factors. Additionally the cross-linking ability of AGEs may result in the formation of abnormal cross-links with proteins, such as plasma proteins and collagen, inducing physical and chemical changes in collagen structure and function such as basement membrane thickening and a resistance to proteolytic digestion (Sell et al., 1992).

Studies have shown that the active formation of AGEs and their accumulation in blood and tissues is dependent on both, the degree and the duration of glycemic control. In fact, follow up studies in the DCCT as well as the UKPDS have demonstrated that strict glycemic control over a period of time during the initial stages of diabetes (both type 2 and type 1, respectively) delayed the progression of complications and even, cardiovascular events (DCCT, 2003; Holman et al., 2008). This phenomenon has been described as a legacy effect or the development of a metabolic memory, wherein strict blood glucose regulation in the initial years of diabetes deferred the vascular complications of diabetes. Notably, recent evidence has implicated accumulated AGEs in the onset of vascular complications (Yamagishi and Imaizumi, 2005; Koska et al., 2018) and may well be involved in the development of a metabolic memory.

Receptor for AGEs (RAGEs)

Several AGE binding molecules such as lactoferrin, galectin-3, CD36 have been described (Thornalley, 1998) that are known to act as AGEs receptors with RAGE (receptor for AGEs) being the most well-known and well characterized one (Prabhakar, 2016). RAGE is a multi-ligand receptor capable of binding diverse ligands including cytokines, amphoterin, integrins and amyloid β peptide and fibrills which can, in turn activate RAGE (Hudson et al., 2003). It belongs to the immunoglobulin superfamily and has five domains, three extracellular domains involved in ligand binding, a transmembrane domain for anchorage and lastly, a fifth intracellular domain that interacts with intracellular mediators (Stern et al., 2002). The expression of RAGE is thought to be increased by the presence of AGEs as well as other ligands mentioned previously. The interaction of AGE-RAGE is thought to be associated with pathogenesis (Taguchi et al., 1999) acting by various mechanisms affecting cellular signaling, including increased cytokine and adhesion molecule (ICAM) expression, nuclear factor-kB (NF-kB) activation, induction of oxidative stress, increased vascular permeability, and elevated cytosolic ROS, ultimately causing an inflammatory response (Naka et al., 2004; Piarulli et al., 2012).

A splice variant of RAGE, known as the soluble receptor for AGEs or sRAGE, which is believed to arise from the cleavage of RAGE. Although, the physiological role of this isoform is not completely understood, however, it has been reported to act as a neutralizer of AGE-mediated damage by competing with cell-surface RAGEs for ligand binding, and thus, modulating the AGE-RAGE system (Hanford et al., 2004). Besides, serum levels of sRAGE are reflective of RAGE expression in tissues and thereby, endothelial cell damage; they may also predict the degree of vascular damage (Nakamura et al., 2007).

Indeed, the oxidative stress and inflammation caused by the AGE-RAGE system inactivates endothelial Nitric Oxide Synthase and increases expression of NADPH oxidase causes endothelial cell dysfunction and aggravation of thrombotic tendency (Xu et al., 2005; Yamagishi et al., 2015). The increased NADPH oxidase exacerbates the oxidative stress

while amplifying AGE production and RAGE expression (Cheng et al., 2012). Additionally, the creation of irreversible cross-links by AGEs along with the pro-inflammatory state and vascular endothelial growth factor (VEGF) production induced by AGE-RAGE interaction causes vascular stiffening and pathological angiogenesis (Treins et al., 2001). This may contribute to the development of vascular complications (Goldin et al., 2006) as evidenced by hyperglycemia-induced increase in expression of RAGE in atherosclerotic plaques of diabetic patients (Prabhakar and Sivakumar, 2019), and the more recent observation that AGEs may promote the differentiation of endothelial cells into osteoblasts leading to the formation of calcified lesions in plaques (Wei et al., 2013). Finally, the sustained activation of the AGE-RAGE has also been implicated in the development of a long-term glycemic memory, wherein AGEs bound to long-lasting proteins like collagen serve as a long-term metabolic memory of hyperglycaemia episodes and oxidative stress (Genuth et al., 2005). Jax (2010) proposed that hyperglycaemia (AGEs) -induced ROS-dependent structural changes in the microvasculature might leave a metabolic imprint that manifests as cardiovascular events. Nevertheless, it is the hyperglycemia accompanied by the increased ROS generation and cytokine production aggravated by AGEs that precipitates cellular death and leads to a chronic low grade inflammatory state responsible for diabetic complications.

AGEs in diabetic retinopathy

This is one of the most important and debilitating complications of diabetes where hyperglycemia causes damage to the retinal microvascular cells, development of abnormal blood vessels and other functional/structural changes. A possible role for AGEs in this progression is evidenced by the accumulation of AGEs in retinal pericytes of diabetic patients (Stitt et al., 1997) possibly impairing both their function and survival (Sharma et al., 1995). In addition, vascular damage may also manifest due to platelet aggregation, endothelial dysfunction, hypertension and induction of vascular endothelial growth factor (Antonietti et al., 2006). More recently, another aspect that has been discussed is neuronal damage that might also contribute to the pathogenesis (Mendez et al., 2010). AGEs have been postulated to play a role since their accumulation is reported to impair retinal physiology by rendering Muller macroglia dysfunctional and various other changes that lead to retinal neural neurotoxicity (Genuth et al., 2005).

AGEs in diabetic neuropathy

Diabetic neuropathy affects both peripheral and autonomic nerves manifesting, for instance, as lower limb morbidity or a cause of sudden death, respectively. Hyperglycemia has been reported to stimulate glycolytic and polyol pathways in peripheral nerves (Wada and Yagihashi, 2005) with demonstrations of the formation and accumulation of AGEs in peripheral nerves in experimental animal models (Wada et al., 2001) and in diabetic patients (Sugimoto et al., 1997). Furthermore, multiple publications have described how AGEs-induced modifications of ECM proteins may lead to basement membrane thickness, whereas the modification of specific proteins may explain the interrupted neuronal transport, nerve fibre demyelination in Schwann cells, atrophy and degeneration of nerve fibre and loss of axonal nerve fibre regeneration (as reviewed by Chilelli et al., 2013). Thus, AGEs may directly impair the structural and functional roles of proteins, directly by glycation and indirectly, by activation of RAGE, and the resulting pathological processes may inflict neural damage, particularly the AGE-RAGE mediated microangiopathy in the peripheral nerve (Wada and Yagihashi, 2005).

AGEs in diabetic nephropathy

Diabetic nephropathy is one of the most commonly encountered complications of diabetes and refers to a progressive decline in kidney function, specifically the glomerular

filtration rate that has been correlated by Genuth and colleagues (2005) with increasing AGEs in circulation. The deleterious effects of these extend to multiple aspects including but not limited to cross-linking of matrix proteins by AGEs and modulation of signaling pathways that contribute to disturbed structural integrity and compromised functionality. The interaction of AGEs with RAGE has been shown to activate signaling pathways that induce apoptosis and lead to the generation of an endogenous inhibitor of NOS contributing to the development and progression of diabetic nephropathy (Ojima et al., 2013). The increased vascular permeability of albumin maybe attributed to the impaired functioning of the glycated collagen while glycation of other structural proteins in the extracellular matrix may prevent their degradation causing accumulation of collagens laminins and fibronectins resulting in the increased basement membrane thickness seen in nephropathy (Forbes et al., 2003). Moreover, diabetic nephropathy is a dual edged sword such that damage is inflicted by increased AGEs formation on the one hand and reduced clearance of serum AGEs on the other (Yamagishi et al., 2010).

2. CONCLUSION

In addition to ROS, AGEs, seem to be key players in the pathogenesis of diabetes-related complications with their modulation of signalling pathways and generation of cytokines and inflammatory molecules. Viewed from an etiologic standpoint, approaches targeting the formation, accumulation and interaction of AGEs may be significant targets in the control of diabetic complications. Several drugs including statins, telmisartin and ramipril and some anti-diabetic drugs are known to modulate AGEs by inhibiting AGEs formation, RAGE expression or post-RAGE signal transduction (Rhee and Kim, 2018). While these recently identified compounds and modulation of metabolic steps as potential therapeutics need further evaluation for their AGE-specific therapeutic potential, they may putatively be developed along with other interventions including glycemic control and AGEs-limited diet for limiting diabetic complications and improving the overall quality of life of diabetics.

REFERENCES:

[1] Antonetti, D. A., Barber, A. J., Bronson, S. K., Freeman, W. M., Gardner, T. W., Jefferson, L. S., Kester, M., Kimball, S.R., Krady, J.K., LaNoue, K.F., Norbury, C. C. (2006). Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes, 55(9), 2401-2411.

[2] Banerjee, M., Khursheed, R., Yadav, A. K., Singh, S. K., Gulati, M., Pandey, D. K., Prabhakar, P.K., Kumar, R., Porwal, O., Awasthi, A. & Kumari, Y. (2020). A Systematic Review on Synthetic Drugs and Phytopharmaceuticals Used to Manage Diabetes. Current Diabetes Reviews, 16(4), 340-356..

[3] Baynes, J. W. (2002). The Maillard hypothesis on aging: time to focus on DNA. Annals of the New York Academy of Sciences, 959(1), 360-367.

[4] Baynes, J. W., & Thorpe, S. R. (1999). Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes, 48(1), 1-9.

[5] Brownlee, M. (1994). Advanced protein glycosylation in diabetes and aging. Annu Rev Med, 154, 2473-2479.

[6] Prabhakar, P. K., Singh, K., Kabra, D., & Gupta, J. (2020). Natural SIRT1 modifiers as promising therapeutic agents for improving diabetic wound healing. Phytomedicine, 153252.

[7] Cheng, C. L., Tang, Y., Zheng, Z., Liu, X., Zengchun, C. Y., Wang, C., & Lou, T. Q. (2012). Advanced glycation end-products activate the renin-angiotensin system through

the RAGE/PI3-K signaling pathway in podocytes. Clinical and Investigative Medicine, E282-E293.

[8] Forbes, J. M., Cooper, M. E., Oldfield, M. D., & Thomas, M. C. (2003). Role of advanced glycation end products in diabetic nephropathy. Journal of the American Society of Nephrology, 14(suppl 3), S254-S258.

[9] Genuth, S., Sun, W., Cleary, P., Sell, D. R., Dahms, W., Malone, J., Sivitz, W., & Monnier, V. M. (2005). Glycation and carboxymethyllysine levels in skin collagen predict the risk of future 10-year progression of diabetic retinopathy and nephropathy in the diabetes control and complications trial and epidemiology of diabetes interventions and complications participants with type 1 diabetes. Diabetes, 54(11), 3103-3111.

[10] Giardino, I., Edelstein, D., & Brownlee, M. (1994). Nonenzymatic glycosylation in vitro and in bovine endothelial cells alters basic fibroblast growth factor activity. A model for intracellular glycosylation in diabetes. The Journal of clinical investigation, 94(1), 110-117.

[11] Goldin, A., Beckman, J. A., Schmidt, A. M., & Creager, M. A. (2006). Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation, 114(6), 597-605.

[12] Hammes, H. P., Alt, A., Niwa, T., Clausen, J. T., Bretzel, R. G., Brownlee, M., & Schleicher, E. D. (1999). Differential accumulation of advanced glycation end products in the course of diabetic retinopathy. Diabetologia, 42(6), 728-736.

[13] Hanford, L. E., Enghild, J. J., Valnickova, Z., Petersen, S. V., Schaefer, L. M., Schaefer, T. M., Reinhart, T.A., & Oury, T. D. (2004). Purification and characterization of mouse soluble receptor for advanced glycation end products (sRAGE). Journal of Biological Chemistry, 279(48), 50019-50024..

[14] Hofmann, M. A., Drury, S., Fu, C., Qu, W., Taguchi, A., Lu, Y., Avila, C., Kambham, N., Bierhaus, A., Nawroth, P., & Neurath, M. F. (1999). RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell, 97(7), 889-901.

[15] Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. New England journal of medicine, 359(15), 1577-1589.

[16] Hudson, B. I., Bucciarelli, L. G., Wendt, T., Sakaguchi, T., Lalla, E., Qu, W., Lu, Y., Lee, L., Stern, D.M., Naka, Y., & Ramasamy, R. (2003). Blockade of receptor for advanced glycation endproducts: a new target for therapeutic intervention in diabetic complications and inflammatory disorders. Archives of biochemistry and biophysics, 419(1), 80-88.

[17] Jax, T. W. (2010). Metabolic memory: a vascular perspective. Cardiovascular diabetology, 9(1), 1-8.

[18] Koska, J., Saremi, A., Howell, S., Bahn, G., De Courten, B., Ginsberg, H., Beisswenger, P.J. & Reaven, P. D. (2018). Advanced glycation end products, oxidation products, and incident cardiovascular events in patients with type 2 diabetes. Diabetes care, 41(3), 570-576.

[19] Liu, G., Zong, G., Hu, F. B., Willett, W. C., Eisenberg, D. M., & Sun, Q. (2017). Cooking methods for red meats and risk of type 2 diabetes: a prospective study of US women. Diabetes Care, 40(8), 1041-1049.

[20] Luevano-Contreras, C., & Chapman-Novakofski, K. (2010). Dietary advanced glycation end products and aging. Nutrients, 2(12), 1247-1265.

[21] Luévano-Contreras, C., Garay-Sevilla, M. E., Wrobel, K., Malacara, J. M., & Wrobel, K. (2012). Dietary advanced glycation end products restriction diminishes inflammation

markers and oxidative stress in patients with type 2 diabetes mellitus. Journal of clinical Biochemistry and Nutrition, 12-40.
[22] Méndez, J. D., Xie, J., Aguilar-Hernández, M., & Méndez-Valenzuela, V. (2010). Molecular susceptibility to glycation and its implication in diabetes mellitus and related diseases. Molecular and cellular biochemistry, 344(1-2), 185-193.
[23] Miura, J., Uchigata, Y., Yamamoto, Y., Takeuchi, M., Sakurai, S., Watanabe, T., Yonekura, H., Yamagishi, S.I., Makita, Z., Sato, A. & Omori, Y. (2004). AGE down-regulation of monocyte RAGE expression and its association with diabetic complications in type 1 diabetes. Journal of diabetes and its complications, 18(1), 53-59.
[24] Nakamura, K., Yamagishi, S. I., Adachi, H., Kurita-Nakamura, Y., Matsui, T., Yoshida, T., & Imaizumi, T. (2007). Serum levels of sRAGE, the soluble form of receptor for advanced glycation end products, are associated with inflammatory markers in patients with type 2 diabetes. Molecular Medicine, 13(3-4), 185-189.
[25] Ojima, A., Ishibashi, Y., Matsui, T., Maeda, S., Nishino, Y., Takeuchi, M., Fukami, K. & Yamagishi, S. I. (2013). Glucagon-like peptide-1 receptor agonist inhibits asymmetric dimethylarginine generation in the kidney of Streptozotocin-induced diabetic rats by blocking advanced glycation end product–induced protein arginine methyltranferase-1 expression. The American journal of pathology, 182(1), 132-141.
[26] Piarulli, F., Sartore, G., & Lapolla, A. (2013). Glyco-oxidation and cardiovascular complications in type 2 diabetes: a clinical update. Acta diabetologica, 50(2), 101-110.
[27] Poulsen, M. W., Hedegaard, R. V., Andersen, J. M., de Courten, B., Bügel, S., Nielsen, J., Skibsted, L.H. & Dragsted, L. O. (2013). Advanced glycation endproducts in food and their effects on health. Food and Chemical Toxicology, 60, 10-37.
[28] Pugliese, G. (2008). Do advanced glycation end products contribute to the development of long-term diabetic complications?. Nutrition, Metabolism and Cardiovascular Diseases, 18(7), 457-460.
[29] Rhee, S. Y., & Kim, Y. S. (2018). The role of advanced glycation end products in diabetic vascular complications. Diabetes & metabolism journal, 42(3), 188-195.
[30] Sato, T., Iwaki, M., Shimogaito, N., Wu, X., Yamagishi, S. I., & Takeuchi, M. (2006). TAGE (toxic AGEs) theory in diabetic complications. Current Molecular Medicine, 6(3), 351-358.
[31] Prabhakar, P. K. (2016). Pathophysiology of secondary complications of diabetes mellitus. Asian J Pharm Clin Res, 9(1), 32-36.
[32] Prabhakar, P. K., & Sivakumar, P. M. (2019). Protein tyrosine phosphatase 1B inhibitors: A novel therapeutic strategy for the management of type 2 diabetes mellitus. Current pharmaceutical design, 25(23), 2526-2539.
[33] Sell, D. R., Lapolla, A., Odetti, P., Fogarty, J., & Monnier, V. M. (1992). Pentosidine formation in skin correlates with severity of complications in individuals with long-standing IDDM. Diabetes, 41(10), 1286-1292.
[34] Sharma, A., Shahzad, B., Kumar, V., Kohli, S. K., Sidhu, G. P. S., Bali, A. S., Handa, N., Kapoor, D., Bhardwaj, R., Zheng, B. (2019). Phytohormones regulate accumulation of osmolytes under abiotic stress. Biomolecules, 9(7), 285.
[35] Sharma, N. K., Gardiner, T. A., & Archer, D. B. (1985). A morphologic and autoradiographic study of cell death and regeneration in the retinal microvasculature of normal and diabetic rats. American journal of ophthalmology, 100(1), 51.
[36] Sharma, P., Mehta, M., Dhanjal, D. S., Kaur, S., Gupta, G., Singh, H., Thangavelu, L., Rajeshkumar, S., Tambuwala, M., Bakshi, H.A., Chellappan, D. K. (2019). Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. Chemico-biological interactions, 309, 108720.

[37] Singh, A. (2012). Hydroxyapatite, a biomaterial: its chemical synthesis, characterization and study of biocompatibility prepared from shell of garden snail, Helix aspersa. Bulletin of Materials Science, 35(6), 1031-1038.
[38] Singh, R., Barden, A., Mori, T., & Beilin, L. (2001). Advanced glycation end-products: a review. Diabetologia, 44(2), 129-146.
[39] Singh, S., Kumar, V., Chauhan, A., Datta, S., Wani, A. B., Singh, N., & Singh, J. (2018). Toxicity, degradation and analysis of the herbicide atrazine. Environmental chemistry letters, 16(1), 211-237.
[40] Singh, S., Singh, N., Kumar, V., Datta, S., Wani, A. B., Singh, D., Singh, K., Singh, J. (2016). Toxicity, monitoring and biodegradation of the fungicide carbendazim. Environmental chemistry letters, 14(3), 317-329.
[41] Stern, D. M., Du Yan, S., Yan, S. F., & Schmidt, A. M. (2002). Receptor for advanced glycation endproducts (RAGE) and the complications of diabetes. Ageing research reviews, 1(1), 1-15.
[42] Stitt, A. W., Li, Y. M., Gardiner, T. A., Bucala, R., Archer, D. B., & Vlassara, H. (1997). Advanced glycation end products (AGEs) co-localize with AGE receptors in the retinal vasculature of diabetic and of AGE-infused rats. The American journal of pathology, 150(2), 523.
[43] Sugimoto, K., Nishizawa, Y., Horiuchi, S., & Yagihashi, S. (1997). Localization in human diabetic peripheral nerve of Nε-carboxymethyllysine-protein adducts, an advanced glycation endproduct. Diabetologia, 40(12), 1380-1387.
[44] Tandon, R., Luxami, V., Dosanjh, H. S., Tandon, N., & Paul, K. (2018). Insulin therapy for diabetes epidemic: a patent review. Current drug delivery, 15(6), 777-794.
[45] Tandon, R., Singh, I., Luxami, V., Tandon, N., & Paul, K. (2019). Recent advances and developments of in vitro evaluation of heterocyclic moieties on cancer cell lines. The Chemical Record, 19(2-3), 362-393.
[46] Tandon, R., Tandon, N., Gupta, N., & Gupta, R. (2018). Art of synthesis of desired polymorphs: A review. Asian J. Chem, 30, 5-14.
[47] Thornalley, P. J. (1998). Cell activation by glycated proteins. AGE receptors, receptor recognition factors and functional classification of AGEs. Cellular and molecular biology (Noisy-le-Grand, France), 44(7), 1013-1023.
[48] Treins, C., Giorgetti-Peraldi, S., Murdaca, J., & Van Obberghen, E. (2001). Regulation of vascular endothelial growth factor expression by advanced glycation end products. Journal of Biological Chemistry, 276(47), 43836-43841.
[49] Turk, Z., Ljubic, S., Turk, N., & Benko, B. (2001). Detection of autoantibodies against advanced glycation endproducts and AGE-immune complexes in serum of patients with diabetes mellitus. Clinica Chimica Acta, 303(1-2), 105-115.
[50] Uribarri, J., Cai, W., Sandu, O., Peppa, M., Goldberg, T., & Vlassara, H. (2005). AGE content of various foods. Ann NY Acad Sci, 1043, 461-6.
[51] Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G.E. & Vlassara, H. (2010). Advanced glycation end products in foods and a practical guide to their reduction in the diet. Journal of the American Dietetic Association, 110(6), 911-916.
[52] Vaid, S. K., Kumar, B., Sharma, A., Shukla, A. K., & Srivastava, P. C. (2014). Effect of Zn solubilizing bacteria on growth promotion and Zn nutrition of rice. Journal of soil science and plant nutrition, 14(4), 889-910.
[53] Vlassara, H. (1996). Advanced glycation end-products and atherosclerosis. Annals of medicine, 28(5), 419-426.

[54] Vyas, M. (2019). Physicochemical analysis of leaves of Eriobotrya japonica and antioxidant and antidiabetic evaluation of its methanolic extract. International Journal of Green Pharmacy (IJGP), 13(3).
[55] Wada, R., & Yagihashi, S. (2005). Role of advanced glycation end products and their receptors in development of diabetic neuropathy. Annals of the New York Academy of Sciences, 1043(1), 598-604.
[56] Wada, R., Nishizawa, Y., Yagihashi, N., Takeuchi, M., Ishikawa, Y., Yasumura, K., Nakano, M. & Yagihashi, S. (2001). Effects of OPB-9195, anti-glycation agent, on experimental diabetic neuropathy. European journal of clinical investigation, 31(6), 513-520.
[57] Wei, Q., Ren, X., Jiang, Y., Jin, H., Liu, N., & Li, J. (2013). Advanced glycation end products accelerate rat vascular calcification through RAGE/oxidative stress. BMC cardiovascular disorders, 13(1), 13.
[58] Usman, B., Sharma, N., Satija, S., Mehta, M., Vyas, M., Khatik, G. L., Khurana, N., Hansbro, P.M., Williams, K. & Dua, K. (2019). Recent developments in alpha-glucosidase inhibitors for management of type-2 diabetes: An update. Current pharmaceutical design, 25(23), 2510-2525.
[59] Wu, C. H., Huang, S. M., Lin, J. A., & Yen, G. C. (2011). Inhibition of advanced glycation endproduct formation by foodstuffs. Food & function, 2(5), 224-234.
[60] Xu, B., Ji, Y., Yao, K., Cao, Y. X., & Ferro, A. (2005). Inhibition of human endothelial cell nitric oxide synthesis by advanced glycation end-products but not glucose: relevance to diabetes. Clinical science, 109(5), 439-446.
[61] Yadav, P., Vyas, M., Dhundi, S., Khedekar, S., Patgiri, B. J., & Prajapati, P. K. (2011). Standard manufacturing procedure and characterisation of Rasasindoora. Int J Ayurvedic Med, 2, 72-80.
[62] Yamagishi, S. I., & Matsui, T. (2010). Advanced glycation end products, oxidative stress and diabetic nephropathy. Oxidative medicine and cellular longevity, 3(2), 101-108.
[63] Yamagishi, S. I., Nakamura, N., Suematsu, M., Kaseda, K., & Matsui, T. (2015). Advanced glycation end products: a molecular target for vascular complications in diabetes. Molecular Medicine, 21(1), S32-S40.
[64] Yamagishi, S., Adachi, H., Takeuchi, M., Enomoto, M., Furuki, K., Matsui, T., Nakamura, K. & Imaizumi, T. (2007). Serum level of advanced glycation end-products (AGEs) is an independent determinant of plasminogen activator inhibitor-1 (PAI-1) in nondiabetic general population. Hormone and Metabolic Research, 39(11), 845-848.